REMARKS

Claims 1-7, 18 and 29-33 are pending. Claims 1 and 4 have been amended. Support for the amendments can be found throughout the application as originally filed. No new matter has been added.

Rejection of Claims 1, 2, 18, 29, 30, 31,32, and 33 Under 35 U.S.C. §112, first paragraph

Claims 1, 2, 18, 29, 30, 31, 32, and 33 are rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification is such a way as to reasonably convey ... that the inventors ... had possession of the claimed invention." Claims 1 and 30 are also rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable a skilled artisan ... to make and/or use the invention." Each of these rejections is discussed below.

With regards to written description of claims 1 and 30, the Examiner states that

> applicants are attempting to obtain greater variability with the actual protein sequence, such variability may be permissible if protein as claimed provides a structure plus function. To meet the functional requirement, the function must be measurable by the ordinary artisan such as ... a given binding activity or substrate turnover. As the claims are written applicant's attempt to identify the functionality as "having the ability to bind fibrillar collagen. This vague definition ... does not provide the requisite function because the ordinary artisan is not sure that binding is even required.

Claim 1, as amended, is directed to an isolated nucleic acid encoding a polypeptide, which among other things, binds to fibrillar collagen. Thus, claim 1, as amended, clearly provides a functional limitation regarding the claimed nucleic acid.

The Examiner also asserts that "the claims have been amended to add sequence identifiers for the von Willabrand factor and factor C using SEQ ID NO's. However, adding these variable sequences 'at least 90%' as claimed does not further limit the claim because the limitations of these factors are themselves vague and unascertainable." In addition to the functional requirement in claim 1 that the encoded polypeptide bind fibrillar collagen, claim 1

recites that the polypeptide have a von Willebrand domain having at least 90% sequence identity to the von Willebrand domain of SEQ ID NO: 4 or SEQ ID NO:5.

Applicants respectfully traverse this portion of the rejection.

The Examiner's concern that the limitations of at least 90% homology to von Willebrand factor A and factor C domains are "vague and unascertainable due to the variability" is incorrect. There is clearly sufficient written description for a nucleic acid which encodes a polypeptide having the combined limitations of at least 90% sequence identity to von Willebrand factor A and factor C domains, at least 90% sequence identity to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:7 and a recited binding activity. The disclosure provides guidance as to the critical structural features of von Willebrand factor A domains and factor C domains. The disclosure also illustrates the degree of homology between these domains within COCH5B2 and other proteins (see Fig. 4 and Fig. 7C). For example, Applicants demonstrate that the factor C domain of human, mouse, and chicken COCH5B2 contains four conserved cysteine residues that are also conserved within the factor C molecule from Limulus (horseshoe crab) (Fig. 7C). The importance of cysteine residues to the three-dimensional structure of extracellular proteins and distinct modules found in extracellular proteins is discussed throughout the specification (see, for example, p.81). Also, Applicants show that missense mutations found in human COCH5B2 that are correlated with a loss of function of COCH5B2, map to the factor C homologous region of the gene. The positions of these residues and the degree of their conservation with the COCH5B2 of mouse and chicken and with the Limulus factor C domain is noted (see, e.g., p. 81-82). In addition, Applicants demonstrate the degree of conservation between the recited von Willebrand factor sequence and other von Willebrand factor sequences and disclose the binding of von Willebrand factor A domains to fibrillar collagen on page73 of the specification. The specification clearly discloses features of von Willebrand factor A and factor C domains that contain variability and those that do not permit variability, thus providing sufficient description, particularly when combined with the added functional limitation. Therefore, Applicants request that the Examiner withdraw the rejection of claim 1.

The Examiner rejects claims 1, 2, 18, 29, 30, 31, 32, and 33 "as containing subject matter which was not described in the specification is such a way as to reasonably convey ... that the inventors ... had possession of the claimed invention" Stating that

> The claims as written ... encompass polynucleotides which vary substantially in length and in nucleotide composition, the genes also include 5' and 3' regulatory elements. The broadly claimed genus additionally encompasses genes as well as genes incorporating only portions of the disclosed sequence.
>
> The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus...The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure or function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure.

Applicants respectfully traverse this rejection. Contrary to the Examiner's assertions, the claims clearly provide sufficient structural and/or functional limitations to indicate that, at the time of filing, Applicants were in possession of the claimed invention.

For instance, claims 1, 2, 30, 32, and 33 are drawn to isolated nucleic acid molecules encoding at a minimum the amino acid sequence of SEQ ID NO:2, SEQ ID NO:7, or a nucleic acid which includes a minimum length of SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:6.

The Revised Interim Written Description Guidelines Training Materials (hereafter referred to as "the Guidelines") clearly indicate that there is sufficient disclosure for the claimed nucleic acid sequences. Applicants direct the Examiner's attention to Example 8 of the Guidelines. Example 8 indicates that the written description requirement for a claim drawn to an isolated nucleic acid molecule comprising a SEQ ID NO. is satisfied where a single species of the SEQ ID NO. is explicitly disclosed and where the SEQ ID NO. is an open reading frame. Since the present application clearly described the open reading frame for both human and mouse COCH5B2, the present application clearly provides sufficient written description for claims 1, 2, 30, 32 and 33. Accordingly, Applicant requests that the rejection of these claims be withdrawn.

The remaining claims recite nucleic acid fragments having at a minimum 1000 nucleotides of the recited nucleic acid sequences or encode at least 75 contiguous amino acid residues of the recited amino acid sequences. It is hard to understand how the present application does not provide sufficient written description for these claims. The claims require that the fragments have the

recited sequences, and thus recite a significant amount of information regarding the structure of the nucleic acids. In addition, as indicated above, the Guidelines provide that a disclosure of the open reading frame is sufficient disclosure for "comprising" language in a claim. Thus, there is sufficient description of the claimed fragments in the present application and Applicants respectfully request that the Examiner withdraw this rejection.

With regards to the enablement of claims 1 and 30, Examiner states that the addition of the sequence identifiers for the von Willebrand and factor C domains does not help limit claim 1 because "the limitations of these factors are themselves vague and unascertainable due to the variability....such variability may be permissible if protein as claimed provides a structure plus function." Claim 1, as amended, indicates that the nucleic acid encodes a polypeptide, which among other things, binds to fibrillar collagen. The specification provides multiple references which describe how one performs binding assays in which interaction of a molecule with fibrillar collagen can be measured (see, e.g., p. 73). Furthermore, binding assays were known in the art at the time of filing. Thus, a skilled artisan could clearly determine if the encoded polypeptide had the recited function without undue experimentation.

As to the Examiner's statements regarding the variability of von Willebrand and factor C domains, the specification clearly refers to features of these domains that do not permit variability and discloses regions of conservation between these domains in COCH5B2 and other molecules. The specification teaches the determination of homology between nucleotide and protein sequences. See, for example, p.24. The disclosure of assays which measure binding of molecules encoded by the claimed nucleic acids as well as the disclosure of methods to ascertain homology provides sufficient enablement.

Claim 30 is drawn to an isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence having at least about 99% sequence identity to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:7. In the specification, Applicant has provided methods of determining homology (see p. 24). Also provided are detailed references to the types of tolerable variations, such as changes that result in conservative amino acid changes, described on p. 24, and allelic variations, described on p. 23. Thus, in view of the explicit disclosure of the

sequences to which the claimed nucleic acid must be 99% homologous (which is a very high level of homology), combined with the discussion of the types of sequences which fall in this range and methods of ascertaining degree of homology, a skilled artisan would clearly be able to make and use the claimed nucleic acids without undue experimentation. Therefore, Applicants respectfully request that the Examiner withdraw the rejections of claims 1 and 30.

Rejection of Claims 1 and 4 Under 35 U.S.C. §112, second paragraph

The Examiner states that claims 1 and 4 are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". In particular, the Examiner states that "the term 'having the ability to bind fibrillar collagen' is indefinite because the ordinary artisan would not know under which circumstances the particular protein would need to/or would not need to bind fibrillar collagen." Claim 1, as amended, recited that the encoded polypeptide binds fibrillar collagen. The amendment therefore obviates the rejection of claim 1.

With respect to claim 4, the Examiner states that the metes and bounds of a "non-COCH5B2" polypeptide are unclear. Claim 4, as amended, is directed to the nucleic acid molecule of claim 1 fused to nucleic acid sequences encoding a non-COCH5B2 polypeptide, thereby clarifying the point at which the molecule becomes a non-COCH5B2 polypeptide.

For the reasons discussed above, Applicant respectfully requests that the Examiner withdraw this rejection.

Rejection of Claim Under the Doctrine of Double Patenting

The Examiner rejects claim 18 under the doctrine of double patenting over claims 17-21 of copending Application No. 09/579288. Upon indication of allowance of one of the claims in either the present application or in the copending application, Applicants will file a terminal disclaimer.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. A check of an appropriate extension of time is being submitted herewith. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 1 and 4 have been amended as follows:

1. (Thrice Amended) An isolated nucleic acid molecule which encodes a polypeptide comprising an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:7 and which encodes a polypeptide having a von Willebrand domain having at least 90% sequence identity to the von Willebrand domain of SEQ ID NO:4 or SEQ ID NO:5, a factor C homologous domain having at least 90% sequence identity to the factor C homologous domain of SEQ ID NO:11, and [having the ability to bind] which binds fibrillar collagen.

4. (Amended) The nucleic acid molecule of claim 1 [further comprising] fused to nucleic acid sequences encoding a non-COCH5B2 polypeptide.